Complete Summary

GUIDELINE TITLE

2002 national guidelines on the management of early syphilis.

BIBLIOGRAPHIC SOURCE(S)

Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD). 2002 national guidelines on the management of early syphilis. London: Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD); 2002. Various p. [94 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Early acquired syphilis (primary, secondary, and early latent)
- Congenital syphilis

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Treatment

CLINICAL SPECIALTY

Infectious Diseases
Obstetrics and Gynecology
Urology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To present national guidelines for the management of early syphilis

TARGET POPULATION

Persons with syphilis including pregnant women, children less than two (2) years of age and individuals with human immunodeficiency virus (HIV) infection

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. Laboratory studies:

   Demonstration of Treponema pallidum by:

   - Dark field microscopy
   - Direct fluorescent antibody (DFA) test
   - Polymer chain reaction (PCR) provided as a reference test

   Serological tests for syphilis:

   - Cardiolipin (reaginic) tests: Venereal Diseases Research Laboratory (VDRL) carbon antigen test/rapid plasma reagin test (RPR)
   - Specific tests: Treponemal enzyme immunoassay (EIA) to detect immunoglobulin G (IgG), immunoglobulins G & M, (IgG & IgM) or immunoglobulin M (IgM), Treponema pallidum haemagglutination test (TPHA), Treponema pallidum particle agglutination test (TPPA), fluorescent treponemal antibody absorption test (FTA-abs)
2. Other studies such as:
   - Lumbar puncture to assess for neurological involvement (cerebrospinal fluid: cells, protein, Venereal Diseases Research Laboratory test)
   - Full blood count, liver function, electrolytes
   - Chest radiograph
   - Ophthalmic assessment (slit lamp)
   - X-rays of long bones
   - Other clinical assessments (e.g., evidence of rash, stigmata of congenital syphilis)

Treatment/Management

1. Antimicrobial therapy:
   - Procaine penicillin G available as Jenacillin O or Jenacillin A
   - Benzathine penicillin
   - Benzyl penicillin
   - Biclinocillin (benethamine penicillin
   - Doxycycline
   - Erythromycin

    - Azithromycin
    - Ceftriaxone
    - Amoxycillin plus probenecid
2. Management of adverse treatment reactions, including use of prednisolone, antipyretics, diazepam, epinephrine, antihistamine, hydrocortisone
3. Management of contacts
4. Follow-up

MAJOR OUTCOMES CONSIDERED

- Control of syphilis
- Late complications of syphilis
- Rate of treatment failure including incidence of serological relapse

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The guideline developers performed a Medline (U.S. National Library of Medicine) search for the years 1965 to 2000 using the keywords "syphilis", "human", "English", "diagnosis", "therapy".

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence:

Ia

- Evidence obtained from meta-analysis of randomised controlled trials

Ib

- Evidence obtained from at least one randomised controlled trial

IIa

- Evidence obtained from at least one well designed controlled study without randomisation

II b

- Evidence obtained from at least one other type of well designed quasi-experimental study

III

- Evidence obtained from well designed non-experimental descriptive studies such as comparative studies, correlation studies, and case control studies

IV

- Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The revision process commenced with authors being invited to modify and update their 1999 guidelines. These revised versions were posted on the website for a 3 month period and comments invited. The Clinical Effectiveness Group and the authors concerned considered all suggestions and agreed on any modifications to be made.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grading of Recommendations:

A (Evidence Levels Ia, Ib)

- Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.

B (Evidence Levels IIa, IIb, III)

- Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.

C (Evidence Level IV)

- Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities.
- Indicates absence of directly applicable studies of good quality.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The initial versions of the guidelines were sent for review to the following:

- Clinical Effectiveness Group (CEG) members
- Chairs of UK Regional GU Medicine Audit Committees who had responded to an invitation to comment on them
- Chair of the Genitourinary Nurses Association (GUNA)
- President of the Society of Health Advisers in Sexually Transmitted Diseases (SHASTD)
- Clinical Effectiveness Committee of the Faculty of Family Planning and Reproductive Health Care (FFP)

Comments were relayed to the authors and attempts made to reach a consensus on points of contention with ultimate editorial control resting with the Clinical Effectiveness Group. Finally, all the guidelines were ratified by the councils of the two parent societies.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions of the levels of evidence (I-IV) and grades of recommendation (A-C) are repeated at the end of the "Major Recommendations" field.

Diagnosis

<u>Demonstration of Treponema pallidum</u>

(From lesions or infected lymph nodes in early syphilis)

- Dark field microscopy
- Direct fluorescent antibody (DFA) test
- Polymer chain reaction (PCR) test (Orle et al., 1996) - provided as a reference test by Genitourinary Infections Reference Laboratory, Public Health Laboratory Service (PHLS), Bristol, United Kingdom. (Direct fluorescent antibody test and polymer chain reaction test can be used for oral or other lesions where contamination with commensal treponemes is likely)

Serological tests for syphilis

- Cardiolipin (reaginic) tests: Venereal Diseases Research Laboratory test (VDRL) carbon antigen test/rapid plasma reagin test (RPR)
- Specific tests: Treponemal enzyme immunoassay (EIA) to detect immunoglobulin G (IgG), immunoglobulins G & M, (IgG & IgM) or immunoglobulin M (IgM), Treponema pallidum haemagglutination test (TPHA), Treponema pallidum particle agglutination test (TPPA), fluorescent treponemal antibody absorption test (FTA-abs)
- Treponemal enzyme immunoassay (preferably IgG & IgM) or Venereal Diseases Research Laboratory/rapid plasma reagin test (VDRL/RPR) and Treponema pallidum haemagglutination test/Treponema pallidum particle agglutination test are recommended for screening (Egglestone & Turner, 2000)
- Request enzyme immunoassay for anti-treponemal IgM (Schmidt, Edjlalipour, & Luger, 2000; Lefevre, Bertrand, & Bauriaud, 1990; Ijsselmuiden et al., 1989; Baker-Zander et al., 1986) if primary syphilis is suspected - IgM is detectable towards the end of second week of infection while IgG is detectable usually in the fourth or fifth week (Luger, 1988)
- A false negative cardiolipin (reaginic) test may occur in secondary or early latent syphilis due to the prozone phenomenon from using undiluted serum
- All the specific tests are almost invariably positive in secondary and early latent syphilis
- A delayed serological response may occur in secondary infection but this is rare - even in the presence of HIV (Anderson et al., 1989; Hicks et al., 1987; Halperin, 1992)
- Always repeat positive tests to confirm the result
- Repeat serological tests in cases of anogenital ulceration at 3 months if initial tests were negative
- Serological tests cannot differentiate from other treponemal infections- for example, yaws

Confirmation or exclusion of neurological, cardiovascular, or ophthalmic involvement

- Lumbar puncture not necessary in secondary/early latent syphilis unless there is clinical evidence of neurological involvement
- Chest radiograph in latent syphilis
- Ophthalmic assessment (slit lamp) may be helpful to differentiate between acquired or congenital syphilis (interstitial keratitis) in cases of latent infection of uncertain duration where congenital syphilis is suspected

Management

General considerations

- A treponemicidal level of antimicrobial should be achieved in the serum, and in the cerebrospinal fluid in the case of neurosyphilis. A penicillin level of >0.018 mg/l is considered treponemicidal (Idsoe, Guthe, & Willcox, 1972), but a higher concentration might be preferable for more rapid elimination of treponemes. The maximal elimination effect is attained at a level of 0.36 mg/l. (Eagle, Fleischman, & Musselman, 1950)
- Duration of treponemicidal levels of antimicrobial should be at least 7 days to cover a number of division times (30-33 hours) of treponemes in early syphilis with a subtreponemicidal interval of not more than 24-30 hours. (Idsoe, Guthe, & Willcox, 1972) Longer duration of treatment is given in late syphilis on the basis of more slowly dividing treponemes in late syphilis. Treponemes may persist despite apparently successful treatment indicating that some treponemes may be "resting" or dividing very slowly. (Collart, Borel, & Durel, 1964; Yobs et al., 1968; Smith et al., 1968; Hardy et al., 1970; Yogeswari & Chako, 1972; Tramont, 1976) To provide a "safety margin" daily parenteral treatment is given for 10 days in early syphilis and 17 days in late syphilis and in early syphilis with neurological involvement. Clinical data are lacking on the optimal dose, duration of treatment, and the long term efficacy of antimicrobials other than penicillin. The recommendations are based mainly on laboratory considerations, biological plausibility, expert opinion, case studies, and past clinical experience. To standardise therapy the above durations are used for this guideline.
- Parenteral rather than oral treatment has been the treatment of choice because therapy is supervised and bioavailability is guaranteed.
- Non-penicillin antibiotics that have been evaluated are tetracyclines including doxycycline and erythromycin. Erythromycin is least effective and does not penetrate the cerebrospinal fluid or placental barrier well. (Kiefer et al., 1955; Philipson, Sabath, & Charles, 1973) Doxycycline has superceded the older tetracyclines; although 100 mg once or twice daily for 14 days is effective (Center for Disease Control, 1998; Harshan & Jayakumar, 1982), failure of the latter regimen for early latent syphilis has been reported. (Zenilman et al., 1993) Newer antitreponemal regimens include azithromycin and ceftriaxone; the latter has good cerebrospinal fluid penetration. They may be considered as treatment options although more data are desirable. Azithromycin 0.5 or 1 g immediately, followed by 500 mg daily for a total of 10 days was effective for early syphilis. (Verdon, Handsfield, & Johnson, 1994; Gruber et al., 2000; Mashkilleyson et al., 1996) In small studies ceftriaxone has been shown to be effective (Steele, 1984; Marra et al., 1992; Hook et al., 1986; Hook, Roddy, & Handsfield, 1988; Kaksambas et al., 1987; Moorthy et al., 1987; Dowell et al., 1992) with dosages starting from 250 mg daily for 10 days but many physicians in the American Emerging Infections Network used 1-2 g intramuscularly or intravenously for varying duration. (Augenbraun & Workowski, 1999)
- The host immune response is important as 60% of untreated patients go through life without developing late complications. (Gjestland, 1955) Cerebrospinal fluid involvement is common in early syphilis. Although both benzathine penicillin and standard regimens of procaine penicillin G do not achieve treponemicidal levels (Mohr et al., 1976; Ducas & Robsob, 1981; Polnikorn et al., 1980; Goldmeier & Waterworth, 1981; Lowhagen, Brorson, & Kaijser, 1983; Goh et al., 1984), cerebrospinal fluid abnormalities are uncommon after treatment of early syphilis. The prevalence of late syphilis

including neurosyphilis remains low indicating that treatment is effective and suggests that host immune responses in early syphilis play an essential part. However, the use of benzathine penicillin rather than procaine penicillin G has been associated with failure in pregnant women (Hardy et al., 1970; Jackson et al., 1962; Mascola, Pelosi, & Alexander, 1984; Donder et al., 1997) and in an immunocompetent patient (Moskovitz et al., 1982), as well as those with concomitant HIV infection. (Johns, Tierney, & Felsenstein, 1987; Berry et al., 1987; Tomberlin et al., 1994; Malone et al., 1995; Schofer et al., 1996; McLeish et al., 1990; Gregory, Sanchez, & Buchness, 1990) A single dose of 2.4 MU benzathine penicillin in asymptomatic neurosyphilis showed a 21% cerebrospinal fluid relapse rate which was twice that of other penicillin preparations. (Smith et al., 1956)

- Procaine penicillin G is available as 'Jenacillin O' which contains procaine penicillin G in aluminium stearate and peanut oil and as 'Jenacillin A' which contains both procaine penicillin G and penicillin G sodium. Recommended dosage of procaine penicillin G is 600 mg/600,000 u. daily in early syphilis and 1.8 to 2.4 g/1.8-2.4 MU daily in late syphilis but would lead to fraction of a ml using Jenacillin A. To make it easier for administration, it is recommended that a slightly higher dosage of procaine penicillin G be given. (See Appendix 1 in the original guideline document)
- Compliance with daily intramuscular injections with procaine penicillin G had been good. (Crowe et al., 1997) This regimen has been the treatment of choice in the United Kingdom. The control of syphilis over the past 50 years in the United Kingdom has been excellent and the fact that late complications of syphilis are uncommon with hardly any report of failures in patients with concomitant HIV infection indicate that this regimen has been effective.
- All patients should be offered screening for other sexually transmitted infections including HIV.
- When there is an outbreak of early syphilis, it is advisable to screen sexually active patients attending Genitourinary Medicine or HIV clinics for syphilis every three months.

Specific Treatment

Incubating Syphilis/Epidemiological Treatment

- First line therapies:
    - Intramuscular Benzathine penicillin 2.4 MU x 1 (Evidence level III, Recommendation grade B)
    - Doxycycline 100 mg twice daily (BD) x 14 days (III, B)
- Second line therapy:
    - Azithromycin 1 g immediately (III, B)

Early Syphilis (Primary, Secondary, and Early Latent)

- First line therapies:
    - Intramuscular Procaine penicillin G 750 mg daily (Jenacillin A 3 ml or Jenacillin O 2.5 ml) x 10 days (Idsoe, Guthe, & Willcox, 1972; Pedrup, 1960; Weiner, Wilybach, & Ludlow, 1951) (III, B)

      If unable to give daily procaine penicillin on the weekend, give either long acting Procaine penicillin G in aluminium stearate (Jenacillin O) 2

MU or long acting Biclinocillin intramuscularly 2 MU (containing benethamine penicillin 1.2 MU) on Friday to cover the weekend.

    - Intramuscular Benzathine penicillin 2.4 MU single dose, or x 2 (day 1 and 8) (Fiumara, 1983; Rolfs et al., 1997) (III, B)
- Penicillin allergy:
    - Doxycycline 100 mg twice daily (BD) x 14 days (III, B)
    - Erythromycin 500 mg four times daily (QDS) x 14 days (Onada, 1979) (III, B)
    - Other options: Azithromycin 500 mg daily x 10 days (Verdon, Handsfield, & Johnson, 1994; Gruber et al., 2000; Mashkilleyson et al., 1996; Steele, 1984; Marra et al., 1992; Hook et al., 1986), or intramuscular ceftriaxone 500mg daily x 10 days (if no anaphylaxis to penicillin)
- Parenteral treatment refused:
    - Amoxycillin 500 mg four times daily (QDS) plus Probenecid 500 mg four times daily (QDS) x 14 days (Onada, 1979; Goldman, 1970) (III, B)
    - As for penicillin allergy

Neurological/Ophthalmic Involvement in Early Syphilis or If Neurosyphilis Cannot Be Excluded

Biological plausibility suggests that regimens that achieve treponemicidal levels of antimicrobial in the cerebrospinal fluid should be the treatment of choice. There is little data on how this translates into long term clinical efficacy. Treat as for neurosyphilis (see the related National Guideline Clearinghouse (NGC) summary 2002 National Guidelines for the Management of Late Syphilis.

Pregnancy:

All pregnant women should be screened for syphilis at the initial antenatal visit (Hurtig et al., 1998). In pregnant women with untreated early syphilis, 70-100% of infants will be infected with stillbirths in up to one third of cases. Patients should be jointly managed with obstetricians and midwives. All pregnant women with positive treponemal serology should be evaluated for clinical evidence of syphilis and treated as for syphilis. To minimize default, treatment may need to be initiated before a confirmatory second serology is available.

Women who had documented treatment for syphilis in the past do not need retreatment during current or subsequent pregnancies if there is no clinical evidence of syphilis and the Venereal Diseases Research Laboratory (VDRL) or rapid plasma reagin (RPR) test titre is negative or serofast in low titre compared to previous results. However it is important that reinfection is excluded by checking the partner, and babies should be followed-up by a paediatrician to exclude congenital syphilis.

- First line therapy:
    - Intramuscular Procaine penicillin G 750 mg (Jenacillin A 3 ml or Jenacillin O 2.5 ml) daily x 10 days (III, B)
    - If unable to give daily procaine penicillin on the weekend, give either long acting Procaine penicillin G in aluminium stearate (Jenacillin O) 2

MU or long acting Biclinocillin intramuscularly 2 MU (containing benethamine penicillin 1.2 MU) on Friday to cover the weekend

- Penicillin allergy:
    - Erythromycin 500 mg four times daily (QDS) x 14 days plus examination, tests and treatment of all babies at birth (see congenital syphilis) (South, Short, & Knox, 1964; Mamunes et al., 1970; Fenton & Light, 1976) (III, B)
    - Other option: Azithromycin 500 mg daily x 10 days plus examination, tests and treatment of all babies at birth
    - Desensitisation to penicillin may be considered followed by first line treatment (see management of late syphilis for desensitisation schedule) (Wendel et al., 1985).
    - Mothers treated with erythromycin or azithromycin may be considered for retreatment with doxycycline after delivery and when breast-feeding is stopped
- Non-compliance suspected:
    - Benzathine penicillin 2.4 MU intramuscularly weekly x 2 (day 1 and 8) (III, B)

Congenital Syphilis

Babies born to mothers treated antenatally for syphilis should be managed jointly with paediatricians.

Diagnosis

Clinical evidence of congenital syphilis: (Stokes, Beerman, & Ingraham, 1944; Hutchinson, 1887; Fiumara & Lessell, 1983)

- Early (first 2 years): rash including condylomata lata, vesiculo-bullous lesions, snuffles, haemorrhagic rhinitis, osteochondritis, periostitis, pseudoparalysis, mucous patches, perioral fissures, hepatosplenomegaly, generalised lymphadenopathy, non-immune hydrops, glomerulonephritis, neurological or ocular involvement, haemolysis, thrombocytopenia.
- Late including stigmata: interstitial keratitis, Clutton's joints, Hutchinson's incisors, mulberry molars, high palatal arch, rhagades, deafness, frontal bossing, short maxilla, protuberance of mandible, saddlenose deformity, sterno-clavicular thickening, paroxysmal cold haemoglobinuria, neurological or gummatous involvement.

Laboratory evidence of congenital syphilis:

- Serological tests should be performed on infant's blood not cord blood
- Serological tests that detect IgG may be positive due to passive transfer of maternal antibodies whether or not the infant is infected (positive tests due to passively transferred antibody should be negative by 6 months)
- A positive anti-treponemal enzyme immunoassay IgM (Schmitz et al., 1994; Stoll et al., 1993) is consistent with a diagnosis of congenital infection
- Always repeat positive tests to confirm results
- A negative IgM test should be repeated at 4, 8 and 12 weeks as the IgM response might be delayed or suppressed

- Quantitative Venereal Diseases Research Laboratory /rapid plasma reagin (VDRL/RPR) test may be useful for diagnosis if the titre is more than two dilutions (fourfold increase) above the mother's titre
- Serological tests can be negative in infants infected in late pregnancy and should be repeated
- Dark field microscopy from early congenital syphilitic lesions or body fluids
- Blood: full blood count, liver function, electrolytes
- Cerebrospinal fluid: cells, protein, Venereal Diseases Research Laboratory (VDRL) test in late congenital syphilis
- X-rays of long bones
- Ophthalmic assessment as indicated

Treatment

- Intravenous benzyl penicillin sodium 100,000 - 150,000 u/kg daily (in divided doses given as 50,000 u/kg 12 hourly in the first 7 days of life and 8 hourly thereafter) x 10 days (III, B)
- Intramuscular procaine penicillin G 50,000 u/kg daily x 10 days (Jenacillin A 0.2 ml/Kg) (III. B)

Follow-up

- Minimum clinical and serological (Venereal Diseases Research Laboratory [VDRL] or rapid plasma reagin [RPR] test) follow-up should be at 3 months, 6 months and 1 year

Other issues

- Older siblings should be screened for congenital syphilis
- Congenital syphilis diagnosed in an older child or in adulthood should be managed as for late syphilis but the parents, all siblings and any sexual partner should be screened for syphilis

Human immunodeficiency virus (HIV) infected patients

Serological tests for syphilis in patients with both syphilis and HIV are generally reliable although false negative tests and delayed appearance of seroreactivity have been reported. (Hicks et al., 1987; Anderson et al., 1989) HIV infected patients with early syphilis may have an increased risk of neurological involvement, unusual neurological manifestations, and higher rate of treatment failure with benzathine penicillin including more frequent serological relapse and lower rate of elimination of treponemes. (Johns, Tierney, & Felsenstein, 1987; Berry et al., 1987; Tomberlin et al., 1994; Malone et al., 1995; Schofer et al., 1996; McLeish et al., 1990; Gregory, Sanchez, & Buchness, 1990; Rolfs et al., 1997; Radolf & Kaplan, 1988; Morgello & Lauter, 1989; Brandon, Boulos, & Morse, 1993; Muster, Hamill, & Baughn, 1990; Lukehart et al., 1988)

There may also be rapid progression to gummatous syphilis. (Dawson, Evans, & Lawrence, 1988; Hay et al., 1990) HIV infected patients also commonly have neurological abnormalities which may be difficult to differentiate from neurosyphilis. It could be argued that treatment for neurosyphilis should be given

to all HIV positive individuals with syphilis so that neurosyphilis is a less likely part of the differential diagnosis if neurological symptoms or signs are currently present or develop subsequently.

Treatment

- As for neurosyphilis (See the related guideline titled 2002 National Guidelines for the Management of Late Syphilis)

Reactions to Treatment

Patients should be warned of possible reactions to treatment. Facilities for resuscitation should be available in the treatment area.

Jarisch-Herxheimer reaction

An acute febrile illness with headache, myalgia, chills, and rigors and resolving within 24 hours. This is common in early syphilis but is usually not important unless there is neurological or ophthalmic involvement or in pregnancy when it may cause fetal distress and premature labour. It is uncommon in late syphilis but can potentially be life threatening if there is involvement of strategic sites (e.g., coronary ostia, larynx, nervous system). Prednisolone can abolish the febrile episode (Gudjonsson & Skog, 1968) but is not proven to ameliorate local inflammation. Nevertheless, severe clinical deterioration in early syphilis with optic neuritis and uveitis has been reported following treatment. As a steroid is also used in the management of these conditions unrelated to syphilis, biological plausibility would suggest that it may help.

Management

- If cardiovascular or neurological involvement including optic neuritis, inpatient management is advisable
- Prednisolone 10-20 mg three times daily for 3 days, starting anti treponemal treatment 24 hours after commencing prednisolone (IV C)
- Antipyretics

Procaine reaction (procaine psychosis, procaine mania, Hoignes syndrome)

This is due to inadvertent intravenous injection of procaine penicillin and may be minimised by the "aspiration technique" of injection. It is characterised by fear of impending death and may cause hallucinations or fits immediately after injection and lasting less than 20 minutes.

Management

- Exclude anaphylaxis
- Calm and verbal reassurance; restraint may be necessary
- If fits, Diazepam 10 mg rectally or 10 mg intravenously at a rate of not more than 5 mg per minute or 10 mg intramuscularly

Anaphylactic shock

Facilities for treatment of anaphylaxis should be available as penicillin is among the commonest cause.

Management

- Epinephrine (Adrenaline) 1:1000 intramuscularly 0.5 ml followed by
- Intramuscular/intravenous antihistamine- e.g., chlorpheniramine 10 mg
- Intramuscular/intravenous hydrocortisone 100 mg

Management of Contacts

- All patients with syphilis should be seen for partner notification, health education, and confirmation of any past treatment history
- For patients with primary syphilis, sexual partners within the past 3 months should be notified as the incubation period is up to 90 days. Partner notification may have to extend to 2 years for patients in secondary syphilis with clinical relapse or in early latent syphilis
- 46-60% of contactable sexual partners of patients and pregnant women with early syphilis also have the infection (Schober et al., 1983; Phaosovasdi et al., 1989)
- Epidemiological treatment for asymptomatic contacts of early syphilis should be considered unless partners are able to attend regularly for exclusion of syphilis. Serological tests for syphilis including enzyme immunoassay IgM or fluorescent treponemal antibody absorption should be performed at the first visit and repeated at 6 weeks and 3 months

Follow-up

The follow-up is for both reinfection and relapse.

- For early syphilis, minimum clinical and serological (Venereal Diseases Research Laboratory (VDRL) or rapid plasma reagin (RPR) test) follow-up should be monthly for 3 months, 6 months, and 1 year
- Early clinical relapse tends to occur in the oral and anal regions
- A sustained two dilution (fourfold) or greater increase in The Venereal Diseases Research Laboratory (VDRL) or rapid plasma reagin (RPR) test titre suggests reinfection or treatment failure
- Specific treponemal tests may remain positive for life following effective treatment; proper documentation is necessary to prevent unnecessary retreatment. Patients should also be given a letter documenting their treatment
- Reinfection or relapse should be retreated preferably with supervised treatment schedules to ensure compliance and sexual partners should be rescreened.
- If the patient remains asymptomatic and the Venereal Diseases Research Laboratory /rapid plasma reagin (VDRL/RPR) test is negative or serofast at one year, the patient may be discharged
- Those with concomitant HIV infection or on non-penicillin treatment should be followed up annually for life

Definitions:

Levels of Evidence:

Ia

- Evidence obtained from meta-analysis of randomised controlled trials

Ib

- Evidence obtained from at least one randomised controlled trial

IIa

- Evidence obtained from at least one well designed controlled study without randomisation

IIb

- Evidence obtained from at least one other type of well designed quasi-experimental study

III

- Evidence obtained from well designed non-experimental descriptive studies such as comparative studies, correlation studies, and case control studies

IV

- Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Grading of Recommendations:

A (Evidence Levels Ia, Ib)

- Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.

B (Evidence Levels IIa, IIb, III)

- Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.

C (Evidence Level IV)

- Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities.
- Indicates absence of directly applicable studies of good quality.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

References open in a new window

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is graded and identified for select recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate management of early syphilis

POTENTIAL HARMS

Reactions to treatment:

Patients should be warned of possible reactions to treatment. Facilities for resuscitation should be available in the treatment area.

- Jarisch-Herxheimer reaction
- Procaine reaction (procaine psychosis, procaine mania, Hoignes syndrome)
- Anaphylactic shock

See the "Major Recommendations" field for more detailed information about adverse treatment reactions and their management.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Clinical data are lacking on the optimal dose, duration of treatment, and the long term efficacy of antimicrobials other than penicillin. Accordingly, the recommendations are based mainly on laboratory considerations, biological plausibility, expert opinion, case studies, and past clinical experience.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

The Clinical Effectiveness Group reminds the reader that guidelines in themselves are of no use unless they are implemented systematically. The following auditable outcome measures are provided:

Response to treatment:

- Resolution of clinical lesions
- A two dilution (fourfold) or greater titre decrease in the cardiolipin (reaginic) tests within 3-6 months after treatment
- For neurosyphilis, the cerebrospinal fluid (CSF) cell count should have decreased by 6 months and the cerebral spinal fluid should be entirely normal by 2 years except for persistent positive specific tests.
- 95% of patients with early syphilis should complete treatment.
- At least 60% of contactable partners should attend for screening and/or treatment.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD). 2002 national guidelines on the management of early syphilis. London: Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD); 2002. Various p. [94 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1999 Aug (revised 2002)

GUIDELINE DEVELOPER(S)

British Association of Sexual Health and HIV - Medical Specialty Society

SOURCE(S) OF FUNDING

Not stated

GUIDELINE COMMITTEE

Clinical Effectiveness Group (CEG)
Syphilis Guidelines Revision Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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Syphilis Guidelines Revision Group: David Lewis (Chairman); Patrick French; Andrew Turner; Hugh Young; Heather Wilson; Jacinta Jenkins; Marcia Burke

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Conflict of interest: None

GUIDELINE STATUS

This is the current release of the guideline. This guideline updates a previously released version.

An update is not in progress at this time.

GUIDELINE AVAILABILITY

Electronic copies: Available in HTML format from the Association for Genitourinary Medicine (AGUM) Web site. Also available in Portable Document Format (PDF) from the Medical Society for the Study of Venereal Diseases (MSSVD) Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- UK national guidelines on sexually transmitted infections and closely related conditions. Introduction. Sex Transm Infect 1999 Aug;75(Suppl 1):S2-3.

Electronic copies: Available in Portable Document Format (PDF) from the Medical Society for the Study of Venereal Diseases (MSSVD) Web site.

The following is also available:

- Revised UK national guidelines on sexually transmitted infections and closely related conditions 2002. Sex Transm Infect 2002;78:81-2

A related guideline is available:

- Management of late syphilis. United Kingdom: Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD); 2002. Various p. See the National Guideline Clearinghouse (NGC) summary.

Print copies: For further information, please contact the journal publisher, BMJ Publishing Group.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on June 15, 2000. The information was verified by the guideline developer on October 13, 2000. This summary was updated on August 5, 2002.

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Date Modified: 11/15/2004